

Complete Summary

GUIDELINE TITLE

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Oct. 62 p. (Technology appraisal guidance; no. 160).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
 METHODOLOGY - including Rating Scheme and Cost Analysis
 RECOMMENDATIONS
 EVIDENCE SUPPORTING THE RECOMMENDATIONS
 BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
 CONTRAINDICATIONS
 QUALIFYING STATEMENTS
 IMPLEMENTATION OF THE GUIDELINE
 INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
 CATEGORIES
 IDENTIFYING INFORMATION AND AVAILABILITY
 DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Osteoporosis
- Osteoporotic fragility fractures

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
 Management
 Prevention
 Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Geriatrics
Internal Medicine
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost effectiveness of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

TARGET POPULATION

Post-menopausal women with primary osteoporosis who have normal calcium levels and/or vitamin D levels and who have not sustained fragility fracture

Note: This guidance does not cover the following:

- Treatment of women who have sustained a clinically apparent osteoporotic fragility fracture
- Use of alendronate, etidronate, risedronate, raloxifene or strontium ranelate for the primary prevention of osteoporotic fragility fractures in women with normal bone mineral density (BMD) or osteopenia
- Use of the above mentioned drugs for the primary prevention of osteoporotic fragility fractures in women who are on long-term systemic corticosteroid treatment

INTERVENTIONS AND PRACTICES CONSIDERED

1. Alendronate
2. Alternative treatment: etidronate, risedronate, or strontium ranelate

Note: Raloxifene was considered but not recommended

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
 - Survival
 - Vertebral or nonvertebral fracture
 - Continuance and compliance
 - Associated effects
 - Health-related quality of life
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the University of Sheffield, School of Health and Related Research (SchARR) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Alendronate, Etidronate, Risedronate, and Raloxifene Search Strategy

Because of the range of interventions and comparators under review, the literature search aimed to identify all literature relating to the prevention and treatment of osteoporosis. The main searches were conducted in May and July 2002, and updated in September and October 2002. The utilities searches were performed in October and November 2002.

Sources Searched

Fourteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature. A list of the databases searched is provided in Appendix 2 of the Assessment Report #1 (see the "Availability of Companion Documents" field).

In addition, the reference lists of relevant articles and sponsor submissions were handsearched, and various health services research-related resources were consulted via the Internet. These resources included health economics and health technology assessment (HTA) organisations, guideline-producing agencies, registers of generic research and trials, and specialist sites. These additional sources are listed in Appendix 3 of the Assessment Report #1 (see the "Availability of Companion Documents" field).

Search Terms

A combination of free-text and thesaurus terms was used. General 'population' search terms (e.g., osteoporosis, bone, density, diseases, fracture, etc) were used in order to identify all potentially relevant studies. 'Intervention' terms were not used in the main searches since it was felt that these might restrict the results and cause possibly relevant articles to be missed. Utilities searches were performed for breast cancer and for osteoporosis fractures as part of the

economic evaluation section of the report. Copies of the Medline search strategies are included in Appendix 4 of the Assessment Report #1 (see the "Availability of Companion Documents" field). Search strategies for the other databases are available on request.

Search Restrictions

No language, date or study-type restrictions were applied to the searches. However, the Biosciences Information Service (BIOSIS) search was performed as title only, and the Citation Indexes searches were limited with brief clinical trials, systematic reviews, guidelines and economics filters, and to title only, in order to keep the number of hits to a sensible level. A randomised controlled trial (RCT) filter, an economics and quality of life evaluations filter, and a systematic reviews filter, were used in the main searches performed in Medline and Embase to assist the identification of articles of these types (see Appendix 5 of the Assessment Report #1 [see the "Availability of Companion Documents" field]). After the searches were completed, because of the large number of references retrieved, only the articles identified using these specific filters, the articles from the databases that were not searched with filters (such as BIOSIS), and the papers found through handsearching etc, were reviewed.

Inclusion and Exclusion Criteria

Inclusion Criteria

- **Participants:** Women with primary osteoporosis who were at least 6 months postmenopausal
- **Interventions:**
 - Bisphosphonates (alendronate, etidronate, and risedronate)
 - Selective oestrogen receptor modulators (SERMs) (raloxifene)
 - Teriparatide (recombinant human parathyroid hormone [1-34])
- **Comparators:**
 - Vitamin D
 - Calcitriol (a vitamin 1 alpha-hydroxylated derivative)
 - Pharmacological doses of calcium
 - Oestrogens (opposed and unopposed)
 - Exercise
 - Placebo
 - No treatment
- **Outcome measures:** Vertebral or nonvertebral fracture, associated effects, quality of life related to the study intervention, continuance and compliance
- **Study design:** Randomised controlled trials. Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

A discussion of outcome measures is presented in section 3.1.2.1 of the Assessment Report #1 (see "Availability of Companion Documents" field.)

Exclusion Criteria

Studies were excluded if they included participants with secondary osteoporosis (e.g., related to therapy with corticosteroids), or drew their participants

exclusively from patients with specific diseases known to affect fracture rates (e.g., Parkinson's disease).

Only published studies (including those only available in abstract form) were included. As unpublished studies are more likely than published studies to demonstrate small or absent treatment effects, it is recognised that this approach is likely to overestimate the true effects of treatment. However, it was not possible in the time available to seek out unpublished studies.

It had originally been intended to include all relevant studies, whatever the language of publication. However, for practical reasons, it was in fact possible only to include those published in English, French, German, Italian or Spanish. This led to the exclusion of one possibly relevant study published only in Japanese.

Sifting

In principle, the references identified by the literature searches were sifted in two stages, being screened for relevance first by title and then by abstract. However, as it was not possible to identify all relevant studies with fracture outcomes from titles alone, the title sifting stage was used essentially to reject studies which were clearly irrelevant. Following this, the abstracts of all studies which used the relevant interventions in the relevant populations were screened (for studies which did not provide abstracts, the full studies were screened). Twenty-eight studies which had been identified by the literature searches were not identified as relevant at the abstract sifting stage, but were identified from other reviews as reporting fracture outcomes. The reason for this was that, as fracture was only a secondary outcome measure in many studies, it was therefore not reported in the abstract.

Refer to Section 3.1 of the Assessment Report #1 (see the "Availability of Companion Documents" field) for more information.

Strontium Ranelate

Search Strategy

Initial clinical effectiveness searches were conducted in September 2004, and updated in March 2005. The utilities searches were performed in October and November 2002.

Sources Searched

Fourteen electronic bibliographic databases were included in the clinical effectiveness searches; these are listed in Appendix 1 of the Assessment Report #2 (see the "Availability of Companion Documents" field). In addition, the reference lists of relevant articles and sponsor submissions were hand searched.

Search Terms

The clinical effectiveness search strategy utilised terms specific to strontium ranelate. A copy of the Medline search strategy is included in Appendix 2 of the

Assessment Report #2 (see the "Availability of Companion Documents" field). Search strategies for the other databases are available on request.

Search Restrictions

No language, date or study-type restrictions were applied to the clinical effectiveness searches.

Inclusion and Exclusion Criteria

Inclusion Criteria

- **Participants:** Postmenopausal women with osteoporosis, with or without previous fracture
- **Intervention:** Strontium ranelate
- **Comparators:**
 - The bisphosphonate alendronate
- **Outcome measures:**
 - Survival
 - Incident vertebral fracture
 - Incident nonvertebral fracture
 - Adverse effects
 - Continuance
 - Compliance
 - Cost
 - Health-related quality of life
- **Study design:**
 - Randomised controlled trials
 - Economic evaluations

Exclusion Criteria

- Studies in which patients were not vitamin D replete and/or had insufficient calcium intake
- Studies considered methodologically unsound in terms of either study design or method used to assess fractures, or which did not report results in the necessary detail

Sifting

The references identified by the literature searches were sifted in three stages, being screened for relevance first by title and then by abstract. Those papers which seemed from their abstracts to be relevant were then read in full. Studies for which abstracts were not available were also read in full.

A discussion of outcome measures is presented in section 3.1.2.1 of the Assessment Report #2 (see "Availability of Companion Documents" field.)

Economic Analyses

Identifying the Studies

The review has drawn on papers identified from a series of systematic searches undertaken for a health technology assessment (HTA) review of treatment for osteoporosis. These include searches of papers reporting economic evaluation of the prevention and treatment of osteoporosis, and those reporting on quality of life associated with the main fracture states, breast cancer and coronary heart disease. Studies were identified through searches of electronic databases, hand searching, citation searching, reference list checking and those known to researchers involved in the HTA review (refer to Appendix 8 in the Assessment Report #1 [see the "Availability of Companion Documents" field]).

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

Alendronate, Etidronate, Risedronate, and Raloxifene

A total of 90 individual randomized controlled trials (RCTs) met the review inclusion criteria; these are listed in Appendix 8 of the Assessment Report #1 (see the "Availability of Companion Documents" field).

Strontium Ranelate

A total of 24 articles related to three trials met the review inclusion criteria. (Refer to Appendix 4 of the Assessment Report #2 [see the "Availability of Companion Documents" field]).

Cost-Effectiveness

The manufacturers and the Assessment Group provided economic models.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology

considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the University of Sheffield, School of Health and Related Research (SchARR) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Data Extraction Strategy

Data were extracted by one reviewer, using customised data extraction forms.

Where available, the following data will be reviewed:

- Incident vertebral fractures
- Incident nonvertebral fractures
- Incident hip fractures
- Incident wrist fractures
- Quality of life
- Associated effects (both adverse and beneficial)
- Continuance and compliance

Quality Assessment Strategy

The methodological quality of all trials which met the inclusion criteria was assessed using the tool developed by Gillespie et al.* This tool was selected because it was intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis.

The quality assessment tool included the following items:

- Adequacy of randomisation, and masking of randomisation
- Blinded assessment of outcomes - whether outcome assessors were blind to subjects' treatment allocation
- Withdrawals - whether the outcomes of people who withdrew were described and included in the analysis
- Comparability of groups at baseline
- Confirmation of diagnosis of hip or other appendicular skeleton fracture
- Method of diagnosis of vertebral fracture

Definitions of the various levels of randomisation and concealment of randomisation derived from Prendiville et al** were incorporated in the tool (see Appendix 6 of the Assessment Report [see the "Availability of Companion Documents" field]).

It is recognised that the quality assessment tool assesses reporting quality, and not necessarily the true methodological quality of each study. However, where trials were reported in more than one publication, the quality score was calculated on the basis of the combined data from all relevant publications.

Blinding of the quality assessors to author, institution or journal was not considered necessary.

The quality assessment of studies included in the review of clinical effectiveness was carried out by one researcher.

*Gillespie W, Avenell A, Henry D, O'Connell D, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. The Cochrane Library (Oxford) **2001 Issue 4 (27p) (27 ref 21 bib) Update Software, online of CD-ROM, updated quarterly, 2001; 2001-2ROM.

**Prendville W, Elbourne D, and Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. British Journal of Obstetrics & Gynaecology 1988; 95 3-16.

Meta-Analysis Strategy

Studies which met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of subjects suffering fractures, as this enabled calculation of the relative risk of subjects in the intervention group developing a new fracture or fractures, compared with subjects in the control group. Studies which reported only numbers of fractures, or fracture rates (i.e., numbers of fractures per hundred or thousand patient years), could not be included in the meta-analyses unless it was possible to obtain from the authors unpublished information on the number of subjects who suffered fractures. The meta-analysis of data relating to numbers of fractures or fracture rates would have violated the basic statistical assumption that the occurrence of one event does not increase the likelihood of a subsequent event, since once a subject has suffered an osteoporotic fracture, the risk of a subsequent fracture increases.

Ideally, only those studies which had fracture as a primary endpoint would have been included in the meta-analyses. However, pragmatically this was not possible as very few studies met this criterion (see Appendix 7 of the Assessment Report #1 [see the "Availability of Companion Documents" field]). Meta-analysis was carried out using Review Manager using the random-effects model, as this both allows generalization beyond the sample of patients represented by the studies included in the meta-analysis and provides wider, more conservative confidence intervals than the fixed-effects model.

Since the endpoint of interest was fracture, it seemed appropriate to include open-label studies.

To ensure comparability, the meta-analyses of vertebral fractures only pooled data from studies which used the same definition of vertebral fracture. Where possible, data were pooled from studies using a definition which required a 20% or greater reduction in anterior, middle or posterior vertebral height: this definition was felt to identify fractures more reliably than a definition which required a 15% or greater reduction.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals,

patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Manufacturers' Models

For proprietary alendronate, compared with no treatment, the manufacturer's model provided an incremental cost-effectiveness ratio (ICER) of 8622 pounds sterling per quality-adjusted life year (QALY) gained for 70-year-old women with a T-score below -2.5 standard deviation (SD).

For etidronate, compared with no treatment, the manufacturer's model provided an ICER of 18,634 pounds sterling per QALY gained for 70-year-old women with a T-score below -2.5 SD.

For risedronate, compared with no treatment, the manufacturer provided data from two models. The ICER derived from the manufacturer's own model was 577 pounds sterling per QALY gained for women aged 74 years. In the second model provided by the manufacturer, which was commissioned from an external body, the ICER was more than 35,000 pounds sterling per QALY gained for all women without a prior osteoporotic fragility fracture and with a T-score of -2.5 SD. However, for women at slightly higher risk of fracture and aged 70 years or older, the corresponding ICER was 13,500 pounds sterling per QALY gained or less.

For raloxifene, compared with no treatment, the manufacturer provided data for different age groups and different risk levels. All of the analyses included the breast cancer benefits. It was not clear how the different risk levels were defined. The ICERs ranged from 12,000 pounds sterling to 22,000 pounds sterling per QALY gained.

For strontium ranelate, compared with no treatment, the manufacturer provided a model developed by an external organisation. The ICER was 45,028 pounds sterling per QALY gained for 65-year-old women with a T-score of -2.5 SD and 26,686 pounds sterling per QALY gained for 80-year-old women with a T-score of -2.5 SD.

The Assessment Group's Model

The Assessment Group provided a cost-utility model with two components (described in detail in the 2005 Strontium Ranelate Assessment Report). As a first step, the model calculated absolute fracture risk from the epidemiological literature on a number of independent clinical risk factors. As a second step, the model applied relative risk (RR) reductions for fracture taken from the meta-analysis carried out by the School of Health and Related Research, University of Sheffield (SchARR) in 2006. A single estimate of efficacy was used for alendronate and risedronate based on pooled data for these two drugs. Following advice from

the Osteoporosis Guideline Development Group (see www.nice.org.uk) it was assumed that RRs remained constant across all ages, T-scores and fracture status.

The Assessment Group's Model: Results for Alendronate

For alendronate priced at 53.56 pounds sterling per year (once-weekly treatment), and when assuming that 24% of women in the first treatment month and 3.5% of women thereafter experienced bisphosphonate-related side effects, the model produced the following results:

- A strategy of risk assessment, dual-energy X-ray absorptiometry (DXA) scanning and treatment with alendronate in women younger than 65 years resulted in an ICER of more than 20,000 pounds sterling per QALY gained.
- A strategy of risk assessment, DXA scanning and treatment with alendronate in women who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below) resulted in an ICER of less than 20,000 pounds sterling per QALY gained for all women aged 70 years or older, and for women aged 65 to 69 years who have an independent clinical risk factor for fracture.

In a sensitivity analysis for alendronate priced at 53.56 pounds sterling per year, acid-suppressive medication was assumed to affect fracture risk. This sensitivity analysis produced the following results:

- A strategy of risk assessment, DXA scanning and treatment with alendronate in women younger than 70 years resulted in an ICER of more than 20,000 pounds sterling per QALY gained.
- A strategy of risk assessment, DXA scanning and treatment with alendronate in women who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below) resulted in an ICER of less than 20,000 pounds sterling per QALY gained for all women aged 70 years or older.

For alendronate priced at 108.20 pounds sterling per year (daily treatment), and when assuming that 24% of women in the first treatment month and 3.5% of women thereafter experienced bisphosphonate-related side effects, the model produced the following results:

- A strategy of risk assessment, DXA scanning and treatment with alendronate in women younger than 70 years resulted in an ICER of more than 20,000 pounds sterling per QALY gained.
- A strategy of risk assessment, DXA scanning and treatment with alendronate in women who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below) resulted in an ICER of less than 20,000 pounds sterling per QALY gained for all women aged 75 years or older and for women aged 70 to 74 years who have an independent clinical risk factor for fracture. For women aged 70 to 74 years but with no independent clinical risk factor, the T-score needs to be -3 SD or below to give an ICER of less than 20,000 pounds sterling per QALY gained.

The Assessment Group's Model: Results for Other Drugs

For risedronate, raloxifene and strontium ranelate, analyses were conducted to explore identification and treatment strategies that could be cost effective for these interventions when compared with no intervention. All results showed less favourable cost effectiveness than non-proprietary alendronate.

Consideration of the Evidence

Alendronate

The Committee concluded that alendronate (based on the price of 53.56 pounds sterling per year for once-weekly treatment) would be an appropriate use of National Health Service (NHS) resources for the treatment of postmenopausal women who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below) who are aged 65 years or older and who have at least one independent clinical risk factor for fracture.

The Committee considered postmenopausal women below the age of 65 years for whom opportunistic identification was not normally cost effective. The Committee concluded that women under 65 years of age with rheumatoid arthritis, ankylosing spondylitis, Crohn's disease or any condition that has resulted in prolonged immobility, provided that they also have an independent clinical risk factor for fracture, should be considered for DXA scanning, and treated with alendronate if osteoporosis is confirmed.

Considerations for the Other Drugs under Appraisal

The Committee noted that risedronate, etidronate, raloxifene and strontium ranelate were dominated by alendronate (based on the price of 53.56 pounds sterling per year for alendronate); that is, these drugs have a higher acquisition cost than alendronate, but are not more efficacious.

The Committee concluded that risedronate could be recommended for women who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate, and who have a combination of T-score, age and number of independent clinical risk factors for fracture where treatment with risedronate resulted in an ICER of less than 20,000 pounds sterling per QALY gained without the consideration of identification costs.

The Committee decided that etidronate should not be recommended in preference to risedronate. However, the Committee agreed that guidance on the use of etidronate should be included in the recommendations, and concluded that etidronate can be recommended as an alternative treatment option for women who cannot take alendronate.

The Committee concluded that strontium ranelate can be recommended for women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate, and who have a combination of T-score, age and number of independent clinical risk factors for fracture where treatment with strontium

raloxifene resulted in an ICER less than 20,000 pounds sterling per QALY gained without the consideration of identification costs.

The Committee noted that treatment with raloxifene did not result in an ICER of less than 20,000 pounds sterling per QALY gained in any age group, even when identification costs were excluded from the modelling. Therefore, the Committee did not consider raloxifene to be a cost-effective use of NHS resources for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

Refer to Sections 4.2 and 4.3 of the original guideline document for details of the economic analyses provided by the manufacturers, the Assessment Group comments, and the Appraisal Committee considerations.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Guidance

This guidance relates only to treatments for the primary prevention of fragility fractures in postmenopausal women who have osteoporosis. Osteoporosis is defined by a T-score* of -2.5 standard deviations (SD) or below on dual-energy X-ray absorptiometry (DXA) scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.

This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered.

National Institute for Health and Clinical Excellence (NICE) is developing a clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (see www.nice.org.uk). This technology appraisal guidance should be read in the context of the clinical guideline.

This guidance does **not** cover the following:

- The treatment of women who have sustained a clinically apparent osteoporotic fragility fracture (for recommendations for the treatment of women with a prior osteoporotic fragility fracture, see the NGC summary of the accompanying NICE technology appraisal, [Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women](#))
- The use of alendronate, etidronate, risedronate, raloxifene or strontium ranelate for the primary prevention of osteoporotic fragility fractures in women with normal bone mineral density (BMD) or osteopenia (that is, women with a T-score* between -1 and -2.5 SD below peak BMD).
- The use of these drugs for the primary prevention of osteoporotic fragility fractures in women who are on long-term systemic corticosteroid treatment.

The latter two groups will be covered within future guidance produced by the Institute.

1. Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups:
 - Women aged 70 years or older who have an independent clinical risk factor for fracture (see below) or an indicator of low BMD (see below) and who are confirmed to have osteoporosis (that is, a T-score* of -2.5 SD or below). In women aged 75 years or older who have two or more independent clinical risk factors for fracture or indicators of low BMD, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.
 - Women aged 65 to 69 years who have an independent clinical risk factor for fracture (see below) and who are confirmed to have osteoporosis (that is, a T-score* of -2.5 SD or below).
 - Postmenopausal women younger than 65 years who have an independent clinical risk factor for fracture and at least one additional indicator of low BMD (see below) and who are confirmed to have osteoporosis (that is, a T-score* of -2.5 SD or below).

When the decision has been made to initiate treatment with alendronate, the preparation prescribed should be chosen on the basis of the lowest acquisition cost available.

2. Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women:
 - Who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate (as defined below) **and**

- Who also have a combination of T-score*, age and number of independent clinical risk factors for fracture as indicated in the following table.

T-scores* (SD) at (or below) Which Risedronate or Etidronate Is Recommended When Alendronate Cannot Be Taken

	Number of Independent Clinical Risk Factors for Fracture		
Age (years)	0	1	2
65-69	Treatment not recommended	-3.5	-3.0
70-74	-3.5	-3.0	-2.5
75 or older	-3.0	-3.0	-2.5

If a woman aged 75 years or older who has two or more independent clinical risk factors for fracture or indicators of low BMD has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

In deciding between risedronate and etidronate, clinicians and patients need to balance the overall proven effectiveness profile of the drugs against their tolerability and adverse effects in individual patients.

3. Strontium ranelate is recommended as an alternative treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women:
 - Who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate (as defined below) **and**
 - Who also have a combination of T-score*, age and number of independent clinical risk factors for fracture (see below) as indicated in the following table.

T-scores* (SD) at (or below) Which Strontium Ranelate Is Recommended When Alendronate and either Risedronate or Etidronate Cannot Be Taken

	Number of Independent Clinical Risk Factors for Fracture		
Age (years)	0	1	2
65-69	Treatment not recommended	-4.5	-4.0
70-74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

4. Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

5. For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.
6. For the purposes of this guidance, indicators of low BMD are low body mass index (defined as less than 22 kg/m²), medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause**.
7. For the purposes of this guidance, intolerance of alendronate, risedronate or etidronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.
8. For the purposes of this guidance, primary prevention refers to opportunistic identification, during visits to a healthcare professional for any reason, of postmenopausal women who are at risk of osteoporotic fragility fractures and who could benefit from drug treatment. It does not imply a dedicated screening programme.
9. Women who are currently receiving treatment with one of the drugs covered by this guidance, but for whom treatment would not have been recommended according to sections above should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

*T-score relates to the measurement of BMD using central (hip and/or spine) DXA scanning, and is expressed as the number of SD from peak BMD.

**Rheumatoid arthritis is also a medical condition indicative of low BMD.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of alendronate, etidronate, risedronate, and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

POTENTIAL HARMS

Adverse Effects of Medications

- Gastrointestinal side effects are common with oral *bisphosphonates*. In people with esophageal abnormalities and other factors that delay esophageal transit or emptying, risedronate should be used cautiously.

- *Raloxifene* is associated with an increased risk of venous thromboembolic events, particularly during the first 4 months of treatment, which is similar to the reported risk associated with hormone replacement therapy.
- The summary of product characteristics states that *strontium ranelate* is not recommended in patients with severe renal impairment and that it should be used with caution in patients at increased risk of venous thromboembolism (VTE). Treatment with strontium ranelate should be discontinued during treatment with oral tetracycline or quinolone antibiotics. The absorption of strontium ranelate is reduced by food, milk and products derived from milk.

For full details of side effects and contraindications, see the summary of product characteristics (SPC) available at <http://emc.medicines.org.uk/>.

CONTRAINDICATIONS

CONTRAINDICATIONS

- *Alendronate* is contraindicated in people with esophageal abnormalities and other factors that delay esophageal transit or emptying.
- *Raloxifene* is contraindicated in people with a history of venous thromboembolism (VTE), hepatic impairment, cholestasis, severe renal impairment, unexplained uterine bleeding or endometrial cancer. Raloxifene should not be co-administered with systemic oestrogens, and in patients with breast cancer it should not be used for osteoporosis treatment or prevention until treatment of the breast cancer, including adjuvant treatment, has been completed.

For full details of side effects and contraindications, see the summary of product characteristics (SPC) available at <http://emc.medicines.org.uk/>.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organizations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by the National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare Standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (www.nice.org.uk//TA160) (see also the "Availability of Companion Documents" field).
 - Slides highlighting key messages for local discussion
 - Costing report and costing template to estimate the savings and costs associated with implementation
 - Audit support for monitoring local practice

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides
Resources
Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Oct. 62 p. (Technology appraisal guidance; no. 160).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Oct

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor Keith Abrams (2006–2008), Professor of Medical Statistics, University of Leicester; Ms Julie Acred (2004–2005), Chief Executive, Derby Hospitals NHS Foundation Trust; Dr Ray Armstrong (2008), Consultant Rheumatologist, Southampton General Hospital; Dr Jeff Aronson (2006–2008), Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford; Dr Darren Ashcroft (2004–2008), Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Professor David Barnett (2004–2008), Professor of Clinical Pharmacology, University of Leicester; Dr Peter Barry (2004–2008), Consultant in Paediatric Intensive Care, Leicester Royal Infirmary; Professor Stirling Bryan (2006–2008) Head, Department of Health Economics, University of Birmingham; Mr Brian Buckley (2004–2006), Vice Chairman, InContact; Professor John Cairns (2006–

2008,) Public Health and Policy, London School of Hygiene and Tropical Medicine; Professor David Chadwick (2005–2006), Professor of Neurology, Walton Centre for Neurology and Neurosurgery; Dr Peter I Clark (2004–2006), Honorary Chairman, Association of Cancer Physicians; Ms Donna Covey (2004–2005), Chief Executive, Asthma UK; Dr Mike Davies (2004–2008), Consultant Physician, University Department of Medicine and Metabolism, Manchester Royal Infirmary; Mr Richard Devereaux-Phillips (2004–2006), Public Affairs Manager, Medtronic Ltd; Professor Jack Dowie (2004–2008), Health Economist, London School of Hygiene and Tropical Medicine; Professor Trisha Greenhalgh (2004–2005), Professor of Primary Health Care, University College London; Lynn Field (2006–2008), Nurse Director, Pan Birmingham Cancer Network; Professor Gary A Ford (2004–2005), Professor of Pharmacology of Old Age/Consultant Physician, Royal Victoria Infirmary, Newcastle upon Tyne; Professor Christopher Fowler (2006–2008), Professor of Surgical Education, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London; Dr Fergus Gleeson (2004–2008), Consultant Radiologist, Churchill Hospital, Oxford; Ms Sally Gooch (2004–2008), Independent Nursing and Healthcare Consultant; Mrs Barbara Greggains (2006–2008), Lay member; Mr Sanjay Gupta (2005–2008), Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust; Ms Linda Hands (2004–2005), Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford; Professor Philip Home (2005–2006), Professor of Diabetes Medicine, University of Newcastle upon Tyne; Dr Peter Jackson (2005–2006) Clinical Pharmacologist, University of Sheffield; Professor Peter Jones (2004–2006), Professor of Statistics and Dean, Faculty of Natural Science, Keele University; Professor Robert Kerwin (2004–2005), Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London; Dr Mike Laker (2005–2007), Medical Director, Newcastle Hospitals NHS Trust; Ms Joy Leavesley (2004), Senior Clinical Governance Manager, Whittington Hospital; Dr Ruth Lesirge (2004), Lay member; Ms Rachel Lewis (2004–2006), Nurse Adviser to the Department of Health; Mr Terence Lewis (2006–2008), Lay member; Dr George Levvy (2005–2006), Lay member; Professor Gary McVeigh (2006–2008), Professor of Cardiovascular Medicine, Queens University, Belfast; Professor Jonathan Michaels (2004–2006), Professor of Vascular Surgery, University of Sheffield; Dr Ruairidh Milne (2004–2008), Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology, University of Southampton; Dr Neil Milner (2004–2008), General Practitioner, Tramways Medical Centre, Sheffield; Dr Rubin Minhas (2004–2008), General Practitioner, CHD Clinical Lead, Medway PCT; Dr John Pounsford (2006–2008), Consultant Physician, Frenchay Hospital, Bristol; Dr Rosalind Ramsay (2006–2008), Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London; Dr Christa Roberts (2006–2008), UK Country Manager, Abbott Vascular; Dr Stephen Saltissi (2006–2008), Consultant Cardiologist, Royal Liverpool University Hospital; Mr Miles Scott (2004–2006), Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust; Dr Lindsay Smith (2005–2008), General Practitioner, East Somerset Research Consortium; Mr Roderick Smith (2006–2008), Finance Director, West Kent PCT; Mr Cliff Snelling (2006–2008), Lay member; Mr Malcolm Stamp (2004), Chief Executive, Addenbrooke's NHS Trust; Professor Ken Stein (2004–2008), Professor of Public Health, Peninsula College of Medicine and Dentistry, University of Exeter; Professor Andrew Stevens (Chair) (2004–2008), Professor of Public Health, University of Birmingham; Dr Rod Taylor (2006–2008), Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter & Plymouth

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Oct. 4 p. (Technology appraisal 160). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. Costing template and report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Nov. Various p. (Technology appraisal 160). Available in Portable Document Format (PDF) from the [NICE Web site](#).
- Primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. Slide set. Costing template and report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008. 21 p. (Technology appraisal 160). Available in Portable Document Format (PDF) from the [NICE Web site](#).
- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Audit support. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008. 9 p. (Technology appraisal 160). Available in Portable Document Format (PDF) from the [NICE Web site](#).
- The clinical effectiveness and cost effectiveness of prevention and treatment of osteoporosis. Assessment report #1. 427 p. Available in Portable Document Format (PDF) from the [NICE Web site](#).
- The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Assessment report #2. 164 p. Available in Portable Document Format (PDF) from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1723. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Alendronate, etidronate, risedronate, strontium ranelate and raloxifene for preventing bone fractures in postmenopausal women with osteoporosis who have not had a fracture. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Oct. 6 p. (Technology appraisal 160). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1724. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI Institute on May 13, 2009.

The National Institute for Health and Clinical Excellence (NICE) has granted the National Guideline Clearinghouse (NGC) permission to include summaries of their Technology Appraisal guidance with the intention of disseminating and facilitating the implementation of that guidance. NICE has not verified this content to confirm that it accurately reflects the original NICE guidance and therefore no guarantees are given by NICE in this regard. All NICE technology appraisal guidance is prepared in relation to the National Health Service in England and Wales. NICE has not been involved in the development or adaptation of NICE guidance for use in any other country. The full versions of all NICE guidance can be found at www.nice.org.uk.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at <http://www.guideline.gov/about/inclusion.aspx>.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

[Copyright/Permission Requests](#)

Date Modified: 6/1/2009

